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Long-term stable lung function and second uncomplicated pregnancy on sirolimus in lymphangioleiomyomatosis (LAM)

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Abstract. We present a patient with lymphangioleiomyomatosis (LAM) on long-term sirolimus (now 79 months) who has had a second successful pregnancy. The second pregnancy on uninterrupted low-dose sirolimus (plasma levels 3-5 μg/L) was uncomplicated both with respect to mother and child suggesting that low-dose sirolimus might be safe in selected pregnant patients with stable LAM. The long-term time course in this patient is in agreement with recent reports of a long-term beneficial effect of sirolimus in LAM. In this patient, the pregnancies did not seem to impair the long-term improvement of lung-function on sirolimus. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 259-264)*

Key words: lymphangioleiomyomatosis, lung function, pregnancy, sirolimus

Abbreviations used in the text:
LAM: lymphangioleiomyomatosis; MILES trial: Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus trial; FEV1: forced expiratory volume in 1 second; VC: vital capacity; DCO: diffusing capacity for carbon monoxide; mTOR: mammalian target of rapamycin.

Introduction

We recently reported the case of a successful pregnancy in a patient with lymphangioleiomyomatosis (LAM) (1). In the following, we report the further outcome on sirolimus including a second successful pregnancy in this patient.

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Case presentation

Long-term course

In accordance with results of the MILES (Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus) trial (2), which demonstrated efficacy of sirolimus in stabilizing lung function of LAM, and due to evolving evidence in favor of long-term therapy with sirolimus (3, 4), the patient had been on sirolimus adjusted to maintain blood levels of 5-15 μg/L. The long-term time course of events is illustrated in Figure 1A. In line with the typical natural course of LAM, there had been a rapid decline in lung function with loss of FEV1 and VC with an annual reduction of about 10% before therapy with sirolimus. This was accompanied by an increase of intrathoracic gas volume indicating increasing overinflation (Table 1). An even more pronounced decline was observed in diffusing capacity with a reduction of 50 % in less than three years. There were no pleural effusions. When sirolimus was started,

the patient was severely hypoxemic requiring long-term oxygen therapy continuously. Listing for lung transplantation had been recommended. After start of sirolimus, the decline in lung function was stopped and partially reversed. The improvement continued for about five years of sirolimus therapy with an increase of FEV1 from 56% to around 80% and of diffusing capacity (DCO) from 26% to around 38%. In line with the improved lung function, dyspnea and blood gases improved. From four years after start of sirolimus onwards, the patient has not required oxygen supplementation any more. Having been on sirolimus for more than 6½ years (with exception of 15 weeks off sirolimus during the first pregnancy), the patients is well and shows stable lung function (Table 1).

Pregnancies

The detailed time course of events during the two pregnancies is shown in Figure 1B and 1C, respectively. The first pregnancy has been described in detail previously (1). Briefly, sirolimus therapy was interrupted with discovery of the 1st pregnancy (week 7) and resumed at week 23 because of declining lung function. After restart of sirolimus, lung function parameters including diffusing capacity, improved. However, the further course of the 1st pregnancy was complicated by a persistent pneumothorax requiring surgery which was performed after delivery. The first child, a boy born by Caesarian section at 32 weeks, is now 5 years old. He is at the 19th percentile of weight and, according to the mother, may have a slow language development. Results of formal assessments are pending.

Three years and ten months after delivery of the first child, the patient, now 34 years old, reported the second pregnancy, then 7th week. The second pregnancy occurred whilst on sirolimus 3 mg o.d. (trough level 7.3 μg/L). Because lung function had deteriorated after discontinuation of sirolimus during the first pregnancy, it was decided to continue therapy with sirolimus, but at a reduced dose of 2 mg o.d.. In contrast to the first pregnancy, during the second pregnancy (on sirolimus low dose) lung function remained stable (Figure 1C), and no complications occurred. At 32 week + 4, a healthy, normally sized female newborn was delivered by Caesarian section. Since then, the child, now ten months old, has shown a normal development. Routine pediatric assessments did not reveal any abnormalities so far, in particular size and weight are around the 50th percentile.

Sirolimus levels

During non-pregnant times, 2 to 3 mg sirolimus daily were required to maintain blood levels in the low therapeutic range (5-7 μg/L, Table 2) which is in line with previous reports of low-dose sirolimus therapy (5). During pregnancy, a dose of 2 mg daily resulted in declining blood levels below the therapeutic range (Table 2A). Blood levels did not increase after dose adjustment to 3 mg sirolimus daily during the 3rd trimester of the second pregnancy. Overall, sirolimus blood levels were about 40 % lower during pregnancy than at the same dose without pregnancy (Table 2B).

Discussion

In the case presented, the second pregnancy differed from the first pregnancy not only with respect to the uninterrupted sirolimus therapy, but also with respect to lung function which was much better at the start of the second pregnancy. Both factors may have contributed to the uneventful course of the second pregnancy.

In this patient with LAM, the long-term recovery of lung function on sirolimus was not impaired by the two pregnancies. This is noteworthy, since in general, largely based on the occurrence of LAM almost exclusively in women of child-bearing age, LAM has been regarded as a hormone-dependent disease (for review: 6). However, any previous therapeutic approaches using hormone depletion strategies have not been successful. Due to the successful therapy with sirolimus, LAM is now considered to represent a low-grade neoplastic process of smooth muscle cells with the role of hormones still to be defined. Recent *in vitro* data point to a synergistic role of the mTOR pathway and the estrogen stimulated ERK-pathway in the pathogenesis (7).

The cause of the declining levels of sirolimus during pregnancy in this patient is not clear. Sirolimus is a substrate of cytochrome CYP 3A4 (7). Since cytochrome CYP 3A4 activity is increased

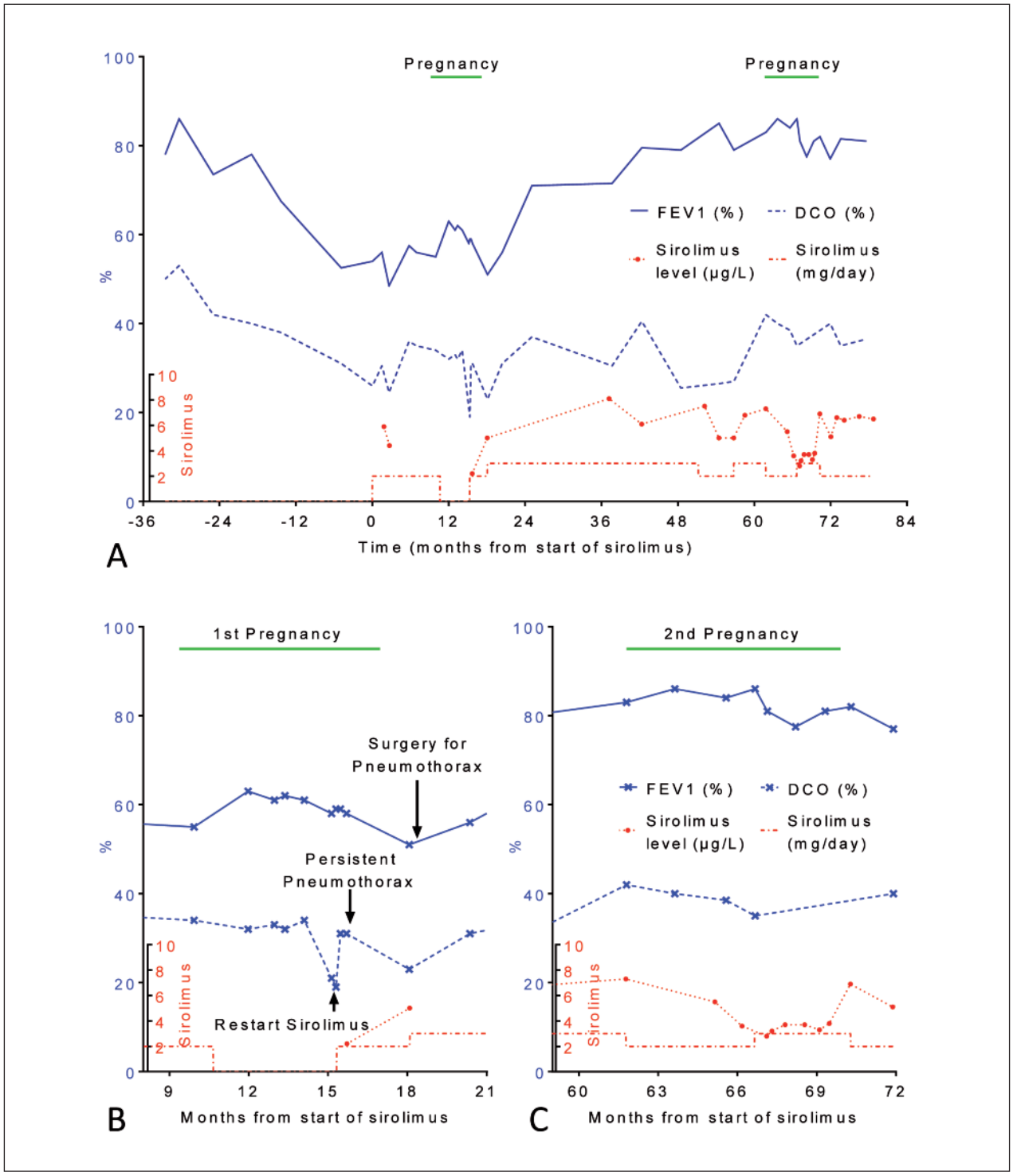

Fig. 1. Time course of pulmonary function parameters (FEV1 and DCO) and of sirolimus dose and blood levels.
A: Time course from 36 months before start of sirolimus until 79 months on sirolimus. Except for measurements during pregnancy, the mean of two consecutive measurements is given. B: Time course and events during the first pregnancy. C: Time course during the uneventful second pregnancy.
FEV1: forced expiratory volume in 1 second; DCO: diffusing capacity for carbon monoxide.

Table 1. Time course of pulmonary function parameters. Except for measurements during pregnancy, mean values of 2-4 consecutive measurements during the period indicated are given. Negative values indicate time periods before start of sirolimus. FEV1: forced expiratory volume in 1 second; VC: vital capacity; TLC: total lung capacity; Rtot: total airway resistance; DCO: diffusing capacity for carbon monoxide

Months (from start of sirolimus)	FEV1 (% expected)	VC (% expected)	ITGV (% expected)	TLC (% expected)	Rtot (kPa*s/L)	DCO (% expected)	Comment
-33 to -30 (n=3)	82	92	102	108	0.19	52	
-30 to -24 (n=2)	83	86	106	111	0.20	48	
-24 to -18 (n=2)	74	92	113	108	0.20	42	
-18 to -12 (n=2)	74	86	103	111	0.22	39	
-12 to -6 (n=2)	65	82	124	112	0.27	31	
-6 to 0 (n=2)	56	69	121	107	0.28	26	
0							Start sirolimus
1 to 3 (n=3)	54	71	-	112	0.36	27	
3 to 8 (n=3)	56	74	-	124	0.32	33	
9.4							Start 1st pregnancy
9.9	55	68	-	122	0.50	34	
12.0	63	100	153	143	0.27	32	Pause sirolimus
13.0	61	69	-	99	0.29	33	
13.4	62	80	140	117	0.25	32	
14.1	61	79	130	101	0.22	34	
15.1	58	71	108	87	0.25	21	
15.3	59	67	114	95	0.40	19	Restart sirolimus
15.5	59	68	108	85	0.29	31	
15.7	58	57	121	91	0.33	31	
17.0							Delivery 1st child
18.1	51	55	140	-	0.22	23	
20.4	56	58	-	90	0.33	31	
25.0	71	83	-	94	0.30	37	
30-36 (n=2)	72	77	-	92	0.30	26	
36-42 (n=3)	75	92	108	95		40	
42-48 (n=2)	81	97	109	93	0.23	38	
48-54 (n=2)	82	96	108	87	0.23	26	
54-61.8 (n=3)	81	97	111	95	0.27	32	
61.8							Start 2nd pregnancy
63.60	86	94	122	92	0.28	40	
65.20	82	97	122	89	0.31	37	
66.15	87	88	117	103	0.31	39	
67.10	81	95	104	84	0.34	32	
67.80	77	88	94	94	0.30	-	
68.20	78	90	112	96	0.21	-	
69.50	84	93	123	97	0.22	-	
69.90							Delivery 2nd child
70-74 (n=4)	80	94	119	87	0.31	38	
74-79 (n=2)	81	96	125	94	0.30	37	

during pregnancy (9, 10), a faster metabolism of sirolimus during pregnancy may account for the low plasma levels. Interestingly, even at blood levels of sirolimus (3-4 μg/L) considered subtherapeutic in the MILES trial (treatment goal 5-15 μg/L), lung function was preserved during pregnancy in this patient. However, as in this patient, there are reports that sirolimus levels below 5 μg/L may be effective in treating LAM (11). Therefore, a possible way to minimize exposure of the unborn whilst preserving treatment efficacy in LAM might be to aim at sirolimus levels of 3-5 μg/L.

Table 2. Sirolimus dose and blood levels during pregnancy and at non-pregnant times. A. Chronological order. B. Mean blood levels at 2 and 3 mg sirolimus o.d. during pregnancy and at non-pregnant times, respectively.

A

Months (from start of sirolimus)	Comment	Sirolimus (mg o.d.)	Sirolimus level (μg/L)
1-4 (n=2)		2	5.2
15.7 (n=1)	1st pregnancy	2	2.2
18.1 (n=1)		2	5.0
36 to 53 (n=4)		3	6.6
53 to 57 (n=2)		2	5.0
57 to 61.8 (n=2)		3	7.1
65.2 (n=1)	2nd pregnancy	2	5.5
66 to 67 (n=2)	2nd pregnancy	2	3.2
67 to 69.5 (n=5)	2nd pregnancy	3	3.5
70.5 (n=1)		3	6.9
72 to 78 (n=4)		2	6.2

B

Sirolimus (mg o.d.)	Comment	Sirolimus level (μg/L, mean)	Standard error
2 (n=9)	non-pregnant	5.54	0.27
2 (n=4)	pregnant	3.52	0.72
3 (n=7)	non-pregnant	6.79	0.41
3 (n=5)	pregnant	3.54	0.12

Since mTOR, the target of sirolimus, has been shown *in-vitro* to play a role in placental amino-acid transport (12, 13), there was concern that treatment with sirolimus during pregnancy might lead to intrauterine growth retardation. However, the studies used concentrations of sirolimus *in vitro* of approximately 90 μg/L, which is far above the recommended therapeutic range of 5-15 μg/L and even more above the levels of sirolimus during the pregnancies presented (2-5 μg/L). The birth weight of both infants in the case presented was normal for dates. Moreover, in a case series of renal transplant recipients, the reported birth weights after exposure to sirolimus were normal (15).

Since the vast majority of LAM patients are young women with a much improved outcome on sirolimus, a significant number may wish to become pregnant. However, in LAM trials, in particular in the MILES trial, pregnant women have been excluded. Therefore, it is important to systematically collect information on the outcome of LAM during pregnancy. The positive outcome of the pregnancy is in line with several reports and case series of successful pregnancies during sirolimus treatment in organ transplant recipients, mainly in renal transplant patients (12, 13), but also in a liver transplant patient (14). There are no reports on long-term outcome of the development of children with intrauterine exposure to sirolimus in the literature. Besides exposure to sirolimus, the apparently slightly delayed development of the first child in this case presentation may have various other reasons including preterm birth or the still relatively poor lung function of the mother at that time. To answer the question of the long-term effect, children with sirolimus exposure *in utero* need to be followed up and documented systematically, e.g. in registries.

In conclusion, the second pregnancy on uninterrupted low-dose sirolimus was uncomplicated both with respect to mother and child suggesting that low-dose sirolimus might be safe in selected pregnant patients with stable LAM. The long-term time course in this patient is in agreement with recent reports of a long-term beneficial effect of sirolimus in LAM (4). In this patient, the pregnancies did not seem to impair the long-term improvement of lung-function on sirolimus.

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